SUPPORT FOR THE AMENDMENTS

Claims 2-9, 11, 15, 19-28, 31, 34, 39, 41, and 58-60 were previously canceled.

Claims 1 and 38 have been amended.

The amendment of Claims 1 and 38 is supported by the corresponding claims as previously presented and originally filed, as well as page 14 and Examples 1-7 of the specification.

No new matter has been added by the present amendments.

REMARKS

Claims 1, 10, 12-14, 16-18, 29, 30, 32, 33, 35-38, 40, and 42-57 are pending in the present application.

The rejections of: (a) Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49, and 55-57 under 35 U.S.C. §103(a) over Gefter et al (US 6,180,608) in view of Bauer et al (US 2002/039996); and (b) Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49, and 55-57 under 35 U.S.C. §103(a) over Gefter et al in view of Bauer et al and Engel et al (US 5,663,145), are respectfully traversed.

The claimed invention provides, *inter alia*, a **pharmaceutical gel preparation** comprising a mixture of:

(a) D-63153 or a pharmaceutically active salt thereof in lyophilized form at a concentration of from 5 to 50 mg of peptide per ml of the preparation, and

(b) an aqueous solution of sodium chloride at a concentration of from 0.05% to about 0.5% (weight/volume), and

wherein the preparation is suitable for administration after reconstitution of (a) by the mixing of (a) and (b) and after a standing time of up to about 120 minutes subsequent to the mixing of (a) and (b). (see Claim 1)

The Examiner's rejections in this case and even the rebuttal are largely the same as that previously made and maintained. Applicants submit that these rejection remain improper and provide the following remarks for further consideration.

At the outset, the present invention relates to a sustained release pharmaceutical administration form, as well as methods and kits, where the form is a pharmaceutical ***gel*** preparation containing D-63153.

In the Office Action at page 6, lines 18-19, the Examiner states that both Gefter et al and Bauer et al disclose a "pharmaceutical gel formulation incorporating GnRH antagonist." The Examiner makes no attempt to support this allegation. Indeed, there is good reason for this omission in the Examiner's rejection – none of Gefter et al, Bauer et al, and Engel et al disclose or suggest a pharmaceutical gel formulation or preparation. In fact the only recitation of a gel in a positive light is in the name of the inventor of US 5,663,145 ("Engel et al"). Indeed, in paragraphs [0004]-[0007], Bauer et al actually teaches that gels are very bad and are to be avoided, especially for peptides prone to aggregation.

Consistent with this recognition, Gefter et al and Bauer et al disclose the use of a suspension or dispersion rather than a gel formulation. In other words, in Gefter et al and Bauer et al a solid form of the GnRH antagonist is used.

Thus, on page 2, line 30 to page 3, line 9 of the specification, the present invention is described as following:

> It has now surprisingly been found that administration forms with sustained release of active ingredient for pharmaceutically active peptides are obtained by reconstituting a lyophilized peptide compound with a low-concentration inorganic salt solution before administration, with the amount of lyophilized peptide compound being chosen so that the peptide solution or suspension after reconstitution is highly concentrated.
>
> As a possible explanation, it is presumed that under these conditions there is controlled development of aggregates of the peptide compounds, which shows or show delayed dissolution. The result is then the found sustained release of this active ingredient into the circulation. In this case, the formation of the aggregates leads to a colloidal dispersion whose viscosity are influenced by the concentration of the peptide compound, the salt concentration and the standing time after reconstitution.

Further, at page 13, line 13 to page 14, line 2 of the specification, it is further stated:

> Formation of the pharmaceutical formulation of the invention is moreover dependent on the following parameters:
>
> 1. the concentration of the peptide compound in the solution after reconstitution

> 2. the concentration of the inorganic salt in the solvent employed for reconstitution
> 3. the standing time of the solution after reconstitution and the extent of aggregation obtained thereby, which is reflected by the viscosity increase.
>
> The high concentration of the peptide compound leads to aggregation thereof, which can be controlled by adding an inorganic salt solution. The solubility of the peptide compound decreases as the salt concentration increases. The colloidal properties become more prominent than the solution properties, as is clear from the increasing viscosity even as far as a gel. The "gel" in this connection represents a bicoherent system consisting of the peptide aggregate as the solid phase and water as the liquid phase.
>
> The administration forms of the invention for pharmaceutically active peptides with sustained release of active ingredient are always in the form of a gel before administration.

As stated above, none of Gefter et al, Bauer et al, or Engel et al disclose a gel formulation and they also fail to disclose the critical determinants above, including the salt concentration. Further, insufficient motivation is found to compensate for this deficiency in conjunction with the deficiency of Gefter et al in failing to disclose or suggest D-63153.

Gefter et al provides the therapeutic effectiveness of a pharmaceutically active peptide which seeks to be maintained *in vivo* over prolonged time periods to treat hormone-dependent diseases. To this end, Gefter et al disclose a pharmaceutical composition comprising a water-insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound in vivo upon administration of the complex. The peptidic compound of Gefter et al comprises peptides, polypeptides and proteins. The peptidic compound can also comprise an LHRH analogue which may be an LHRH agonist or an LHRH antagonist in a narrower sense, including the exemplary the LHRH antagonists PPI-149, PPI-258 and cetrorelix.

In Gefter et al, the carrier macromolecule comprises cationic carrier macromolecule like poly-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule like polyalcohol derivatives, specifically polysaccharides and more specifically

carboxymethylcellulose, algin, alginate, acetate polymers, acrylic polymers, alkali starch glycolate and others.

In Gefter et al a carrier macromolecule is necessary to permit formation of a sustained release complex where in contrast the claimed invention the sustained release complex is formed after reconstitution of a lyophilized form D-63153 or a pharmaceutically active salt thereof at a concentration of from 5 to 50 mg of peptide per ml of the preparation by mixing this lyophilized form with an aqueous solution of sodium chloride at a concentration of from 0.05% to about 0.5% (weight/volume). Thus, the language of the claim contemplates a distinct structure from that disclosed in Gefter et al, even putting aside the fact that Gefter et al fails to disclose D-63153. The Examiner continues to cite the recitation of "comprising" as somehow overcoming the substantial deficiency in Gefter et al, which uses use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149-CMC is *already a sustained delivery complex*. This is not what is claimed even when "comprising" is accounted for. The claims relate to reconstitution of the lyophilized form of D-63165. Thus, the sodium chloride is added to a structurally and physical distinct composition for a distinct purpose and effect from the claimed invention.

Specifically, in the claimed invention, sodium chloride is used as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt. Moreover, it is again submitted that even the composition is distinct in Gefter et al which does not disclose or suggest D-63153 or a pharmaceutically active salt thereof. Bauer et al does not specifically disclose this reconstitution step. Neither Bauer et al nor Engel et al compensate for this deficiency.

It is again submitted that Gefter et al disclose differing sodium chloride concentrations. The Examiner alleges that Bauer et al disclose a pharmaceutical administration form containing peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate and others.

Bauer et al discloses that peptides have a nature prone to uncontrolled aggregation and that the peptides if administered lead to a concentration-dependent lowering of the bioavailability from the peptide concentration. Bauer at al therefore disclose that addition of a free acid to the easily soluble peptide salt prevents that peptide salts prone to aggregation. The combination of the teaching of Gefter et al and of Bauer et al does not lead to the inventive subject matter.

First, it cannot be overlooked that Bauer et al also does not actually disclose or suggest D-63153. The Examiner cites paragraph [0014] of Bauer et al, which states "The peptides employed are the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix, and the antagonists according to the U.S. Pat. No. 5,942,493 and DE 19911771.3." These references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed. Certainly, there is no reason given in Bauer et al, or any of the cited references that D-63153 can and should be selected or that the addition of sodium chloride in the ranges claimed would provide a gel preparation that can be used for administration.

Applicants wish to further note that the Examiner emphasizes that Bauer et al disclose a pharmaceutical administration form which contains peptides prone to aggregation. Bauer et al provide a teaching to *avoid aggregation* of the peptides whereas the presently claimed invention is a sustained release formulation and consequently involves the aggregation of peptides by reconstitution of lyophilized peptide salts with inorganic salts or acetic acid salts.

These ideas are directly opposed. Indeed, as noted above, Bauer et al attempt to avoid aggregation and further caution against gel formation (see paragraphs [0004]-[0007]).

Reference is again made to page 2, line 30 to page 3, line 9 of the specification, which states:

> It has now surprisingly been found that administration forms with sustained release of active ingredient for pharmaceutically active peptides are obtained by reconstituting a lyophilized peptide compound with a low-concentration inorganic salt solution before administration, with the amount of lyophilized peptide compound being chosen so that the peptide solution or suspension after reconstitution is highly concentrated.
>
> As a possible explanation, it is presumed that under these conditions there is controlled development of aggregates of the peptide compounds, which shows or show delayed dissolution. The result is then the found sustained release of this active ingredient into the circulation. In this case, the formation of the aggregates leads to a colloidal dispersion whose viscosity are influenced by the concentration of the peptide compound, the salt concentration and the standing time after reconstitution.

Thus, the mechanism by which the claimed invention is achieved as compared to the cited are at direct odds and are incompatible. The Examiner makes no attempt to address this deficiency Bauer et al and the incompatibility of the disclosures of Bauer et al and Gefter et al. The Examiner is again reminded that "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

Once again, the teachings of Bauer et al are not relevant to the claims of the present application. It is only when Applicants disclosure is used as a guidepost to reconstitute the claimed invention with the benefit of hindsight that the disclosure of Geftner et al and Bauer et al are combinable. In all other proper circumstances, the skilled artisan would not find modification in the disclosure of Bauer et al to modify the disclosure of Geftner et al at least due to the direct contradiction in the disclosures identified above. Instead of addressing this

deficiency, the Examiner continues to resort to boilerplate reliance upon *In re McLaughlin*. Such treatment by the Examiner is a complete abrogation of the obligations set forth in MPEP §707.07(f), which mandates "Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

Thus, the claimed invention is not obvious in view of the combined disclosures of Geftner et al and Bauer et al, even if taken with Engel et al.

To further illustrate the beneficial results flowing from the claimed invention (note: the concentration of the sodium chloride in the claims has been limited to be commensurate in scope with the evidence in Examples 1-7), Applicants again direct the Examiner's attention to the Examples of the present application. In each of Examples 1-7, D-63153 is reconstituted in a solution of sodium chloride. Indeed, Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride. In Example 2, D-63153 reconstituted in 0.1% sodium chloride is shown to retain absolute bioavailability. Example 3 illustrates the testosterone-suppressing potential of D-63153 reconstituted in 0.1% sodium chloride. Examples 4-7 provide various viscosity studies with D-63153 reconstituted in 0.1% to 0.2% sodium chloride, with Example 7 illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride. Geftner et al and Bauer et al do not disclose or suggest these illustrated effects and, as such, it cannot be fairly considered that such an effect would be expected.

The Examiner attempts to disregard this evidence by arguing that it "cannot be compared" since the data is only for 0.1% NaCl. The Examiner's comments rely upon the Gefter et al reconstitution in 0.9% NaCl; however, for the reasons given above, this concentration of NaCl from Gefter et al is not relevant to the claimed invention as this concentration relates to reconstitution of a complex where PPI-149-CMC is *already a*

sustained delivery complex. This is not what is claimed. The claims relate to reconstitution of the lyophilized form of D-63165. Moreover, with the amendment herein to limit the upper limit of sodium chloride to 0.2%, there is nothing remotely close about the disclosed concentration of sodium chloride in Gefter et al. Indeed, the recited sodium chloride amount in Gefter et al is four-and-a-half times or 450% greater than the upper claimed limit. Certainly no motivation can be found to modify the amount of sodium chloride to arrive at the claimed range.

The Examiner disregards the foregoing in part, again, relying upon boilerplate language cited *In re Schulze* and *In re Geisler*. Just as the blind application of *In re McLaughlin* was improper so to is the reliance upon *In re Schulze* and *In re Geisler*. The data relied upon above appears in the application as filed which was filed along with a declaration attesting to the truth and accuracy of all material recited therein. Accordingly, the weight of the evidence in the specification is the same as that provided in a Declaration under 37 C.F.R. §1.132. Similarly, the unexpected results flowing from the claimed invention is provided, at least, at page 2, lined 30-37 of the specification, which states:

> It has now surprisingly been found that administration forms with sustained release of active ingredient for pharmaceutically active peptides are obtained by reconstituting a lyophilized peptide compound with a low-concentration inorganic salt solution before administration, with the amount of lyophilized peptide compound being chosen so that the peptide solution or suspension after reconstitution is highly concentrated.

Again, "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d

1437, 1439 (Fed. Cir. 1987)" Thus, the experimental data discussed above from the specification clearly illustrates that substantial benefits flowing from the claimed composition, which are enough to rebut even a *prima facie* case of obviousness.

In a further consideration the Examiner refers to the Engel et al, and alleges that the current invention in claims 38, 40, and 42 is obvious. Applicants disagree for the reasons already of record, coupled with the evidence provided above. For sake of completeness, Applicants reassert the following with respect to the kit claims.

Engel et al teach a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The current invention claims in claims 38-42 and 58-60 relate a kit comprising an LHRH antagonist as finished preparation of the peptide compound and a solution of an inorganic salt or acetic acid salt for reconstitution. In view of the foregoing, the combination of the teaching of Gefter et al, Bauer et al, and of Engel et al does not lead to the inventive subject matter of the kit claims.

The Examiner also cited Engel et al as allegedly disclosing a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The presently claimed invention relates to kit comprising an LHRH antagonist as a finished preparation of the peptide compound and a solution of sodium chloride for reconstitution. Applicants submit that a combination of the teaching of Gefter et al, Bauer et al, and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claim as proposed herein for the reasons already provided above.

Applicants further submit that it is a remarkable fact that Engel et al disclose a dosage regimen of the pharmaceutical composition in which lyophilisate ampoules are in the form of an acetate and it is not intended to bring it in a slow release form according to the invention

or are already in a slow release form and such slow release form is an embonate salt (and therefore in a suspended form) or the soluble peptide salt is embedded in microparticles (see column 2, lines 48-67). Such slow release form is not the starting form of the present invention.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

The objections to Figures 3-5 is obviated by the submission of replacement Figures 3-5 and the amendment to the description thereof in the specification. Figures 3-5 have been amended to remove the descriptive text and to correct an inadvertent error in the Y-axis (axis of the ordinate) of Figures 4-5 where the title "Concentrations in [mg/mL]" was incorrectly presented as "Concentrations in [ng/mL]". Support for the amendments to Figures 3-5 and to the expanded description of the drawings in the specification is provided by Examples 6 and 7. Thus, this ground of objection is believed to be moot.

Withdrawal of this ground of objection is requested.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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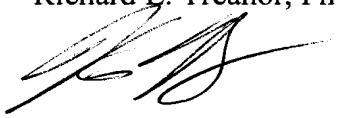

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